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(54) **EXTENDED-RELEASE TOPIRAMATE CAPSULES**

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(58) **Field of Classification Search**

None

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,513,006	A	4/1985	Maryanoff et al.
5,753,693	A	5/1998	Shank
5,753,694	A	5/1998	Shank
5,760,006	A	6/1998	Shank et al.
5,760,007	A	6/1998	Shank et al.
5,935,933	A	8/1999	Shank et al.
5,952,187	A	9/1999	Stenglein et al.
5,998,380	A	12/1999	Ehrenberg et al.
6,071,537	A	6/2000	Shank
6,191,117	B1	2/2001	Kozachuk
6,191,163	B1	2/2001	Cottrell
6,201,010	B1	3/2001	Cottrell
6,214,867	B1	4/2001	Connor
6,319,903	B1	11/2001	Carrazana et al.
6,323,236	B2	11/2001	McElroy
6,340,475	B2	1/2002	Shell et al.
6,362,220	B1	3/2002	Cottrell
6,395,767	B2	5/2002	Robl et al.
6,395,783	B1	5/2002	Dewey et al.
6,414,126	B1	7/2002	Ellsworth et al.
6,420,369	B1	7/2002	Marcotte
6,472,370	B1	10/2002	VanKammem
6,479,467	B1	11/2002	Buchanan et al.
6,486,198	B1	11/2002	Berlant
6,503,884	B1	1/2003	Ehrenberg et al.
6,515,117	B2	2/2003	Ellsworth et al.
6,541,520	B1	4/2003	Dewey et al.
6,544,998	B2	4/2003	Mylari
6,548,529	B1	4/2003	Robl et al.
6,552,000	B2	4/2003	Van Kammen
6,555,519	B2	4/2003	Washburn
6,559,293	B1	5/2003	Almarsson et al.
6,562,865	B1	5/2003	Codd et al.
6,620,819	B2	9/2003	Marcotte
6,622,036	B1	9/2003	Suffin
6,627,653	B2	9/2003	Plata et al.
6,635,280	B2	10/2003	Shell et al.
6,673,815	B2	1/2004	Devasthale et al.
6,683,056	B2	1/2004	Washburn et al.
6,686,337	B2	2/2004	Connor
6,696,091	B2	2/2004	Thakur et al.
6,699,840	B2	3/2004	Almarsson et al.
6,720,348	B2	4/2004	Mylari
6,774,112	B2	8/2004	Gougoutas
6,797,692	B1	9/2004	Ikonomidou
6,875,782	B2	4/2005	Cheng et al.

(Continued)

FOREIGN PATENT DOCUMENTS

EP	1 336 602 A1	8/2003
EP	1 548 024 A1	6/2005

(Continued)

OTHER PUBLICATIONS

U.S. Appl. No. 60/841,924, filed Aug. 31, 2006, Nangia et al.

Al-Tabakha, "HPMC capsules: current status and future prospects," 2010 *J. Pharmacy Pharmaceutical Sci.* 13(3):428-442.

Bialer et al., "Pharmacokinetic interactions of topiramate," 2004 *Clin Pharmacokinet.* 43:763-80.

(Continued)

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(57) **ABSTRACT**

An extended-release topiramate capsule that includes a capsule shell containing a single population of coated particles; wherein each coated particle includes a core and a coating thereon; wherein each particle core includes a homogeneous mixture comprising topiramate throughout its core; and wherein the coating includes one or more release controlling agent(s).

25 Claims, No Drawings

(56) **References Cited**

U.S. PATENT DOCUMENTS

6,890,951 B2 5/2005 Dewey et al.
6,893,661 B1 5/2005 Odidi et al.
6,906,099 B2 6/2005 Dewey et al.
6,908,902 B2 6/2005 Plata et al.
6,921,775 B2 7/2005 Jensen et al.
6,936,590 B2 8/2005 Washburn et al.
6,949,518 B1 9/2005 Chu et al.
6,951,844 B2 10/2005 Hangeland
6,967,212 B2 11/2005 Cheng et al.
6,995,180 B2 2/2006 Magnin et al.
7,018,983 B2 3/2006 Ehrenberg et al.
7,041,650 B2 5/2006 Abdel Magid et al.
7,053,106 B2 5/2006 Cheng et al.
7,056,890 B2 6/2006 Najarian
7,078,526 B2 7/2006 Remenar et al.
7,098,188 B2 8/2006 Abdel Magid et al.
7,109,174 B2 9/2006 Plata-Salaman et al.
7,125,560 B2 10/2006 Thakur et al.
7,196,209 B2 3/2007 Adkins et al.
7,208,477 B2 4/2007 Shapira et al.
7,238,470 B2 7/2007 Hebebrand et al.
7,253,283 B2 8/2007 Weinstein et al.
7,273,881 B2 9/2007 Yang
7,279,485 B2 10/2007 Cheng et al.
7,317,024 B2 1/2008 Yang
7,351,695 B2 4/2008 Almarssoo et al.
7,446,107 B2 11/2008 Remenar et al.
7,498,311 B2 3/2009 Ehrenberg et al.
7,553,818 B2 6/2009 Najarian
7,611,728 B2 11/2009 Kidane et al.
RE41,148 E 2/2010 Burnside et al.
7,659,256 B2 2/2010 Najarian
7,674,776 B2 3/2010 Najarian
7,838,498 B2 11/2010 Chen et al.
7,838,499 B2 11/2010 Chen et al.
7,858,122 B2 12/2010 Kshirsagar et al.
7,884,113 B2 2/2011 Sun et al.
7,897,636 B2 3/2011 Breslav et al.
7,927,613 B2 4/2011 Almarsson et al.
7,947,733 B2 5/2011 Robbins et al.
8,101,592 B2 1/2012 Xie et al.
8,106,021 B2 1/2012 Chen et al.
8,119,621 B2 2/2012 Liotta et al.
8,119,808 B2 2/2012 Sun et al.
8,160,720 B2 4/2012 Wingeier et al.
8,190,270 B2 5/2012 Wingeier et al.
8,298,580 B2 10/2012 Liang et al.
8,652,527 B1 * 2/2014 Betterman et al. 424/489
8,889,190 B2 * 11/2014 Betterman et al. 424/489
2002/0082252 A1 6/2002 Hochman
2002/0169103 A1 11/2002 Dewey et al.
2003/0004176 A1 1/2003 Dewey et al.
2003/0032661 A1 2/2003 Croenlein
2003/0051728 A1 3/2003 Lloyd et al.
2003/0072802 A1 4/2003 Cutler et al.
2003/0091630 A1 5/2003 Louie-Helm et al.
2003/0133951 A1 7/2003 Coe et al.
2003/0133985 A1 7/2003 Louie-Helm et al.
2003/0139332 A1 7/2003 Noble et al.
2003/0203055 A1 10/2003 Rao et al.
2003/0235576 A1 12/2003 Duettmann et al.
2004/0082519 A1 4/2004 Hedner et al.
2004/0082543 A1 4/2004 Cheung
2004/0087513 A1 5/2004 Duettmann et al.
2004/0104501 A1 6/2004 Petereit et al.
2004/0110733 A1 6/2004 Borlak et al.
2004/0115262 A1 6/2004 Jao et al.
2004/0122033 A1 6/2004 Nargund et al.
2004/0142938 A1 7/2004 Sher et al.
2004/0204472 A1 10/2004 Briggs et al.
2004/0229943 A1 11/2004 Hughes et al.
2004/0258758 A1 12/2004 Gustow et al.
2005/0031544 A1 2/2005 Njemanze
2005/0058707 A1 3/2005 Reyes et al.
2005/0070524 A1 3/2005 Stephenson et al.
2005/0095579 A1 5/2005 Thiruvengadam et al.
2005/0119312 A1 6/2005 Cheng et al.
2005/0124533 A1 6/2005 Schatzberg et al.
2005/0129765 A1 6/2005 Li et al.
2005/0136106 A1 6/2005 Sandler
2005/0136108 A1 6/2005 Yam et al.
2005/0169992 A1 8/2005 Jao et al.
2005/0181071 A1 8/2005 Binder
2005/0182049 A1 8/2005 Howard
2005/0182105 A1 8/2005 Nirschl et al.
2005/0203287 A1 9/2005 Batchu et al.
2005/0239839 A1 10/2005 Hamann et al.
2005/0250838 A1 11/2005 Challapalli et al.
2005/0287213 A1 12/2005 Wong et al.
2006/0034927 A1 2/2006 Casadevall et al.
2006/0035914 A1 2/2006 Hochman
2006/0039866 A1 2/2006 Rao et al.
2006/0039867 A1 2/2006 Rao et al.
2006/0058224 A1 3/2006 Yancopoulos et al.
2006/0063722 A1 3/2006 Washburn et al.
2006/0121112 A1 6/2006 Jenkins et al.
2006/0128687 A1 6/2006 Sher et al.
2006/0129324 A1 6/2006 Rabinoff et al.
2006/0142576 A1 6/2006 Meng et al.
2006/0148721 A1 7/2006 Erondu
2006/0160776 A1 7/2006 Stephenson et al.
2006/0160834 A1 7/2006 Fong et al.
2006/0160888 A1 7/2006 Kottayil et al.
2006/0166899 A1 7/2006 Teranishi et al.
2006/0173064 A1 8/2006 Lippa et al.
2006/0199796 A1 9/2006 Chen et al.
2006/0204486 A1 9/2006 Pyke et al.
2006/0204578 A1 9/2006 Vergaz et al.
2006/0211752 A1 9/2006 Kohn et al.
2006/0234950 A1 10/2006 Najarian
2006/0269935 A1 11/2006 Tate et al.
2006/0286163 A1 12/2006 Thakur et al.
2007/0010513 A1 1/2007 Aslanian et al.
2007/0015807 A1 1/2007 Aslanian et al.
2007/0020332 A1 1/2007 Kiel et al.
2007/0026440 A1 2/2007 Broderick et al.
2007/0066644 A1 3/2007 de Lera Ruiz et al.
2007/0066657 A1 3/2007 Tung
2007/0077294 A1 4/2007 Sherman et al.
2007/0099835 A1 5/2007 Qian et al.
2007/0099884 A1 5/2007 Erondu et al.
2007/0099913 A1 5/2007 O'Connor
2007/0111204 A1 5/2007 Delgrosso et al.
2007/0142394 A1 6/2007 Solomon et al.
2007/0167435 A1 7/2007 Mutahi et al.
2007/0173495 A1 7/2007 Palani et al.
2007/0184112 A1 8/2007 Wong et al.
2007/0185056 A1 8/2007 Duan et al.
2007/0185084 A1 8/2007 McKinney et al.
2007/0190043 A1 8/2007 Sych et al.
2007/0191288 A1 8/2007 Shapira et al.
2007/0191289 A1 8/2007 Fushimi et al.
2007/0191371 A1 8/2007 Bennett et al.
2007/0197449 A1 8/2007 Fushimi et al.
2007/0197450 A1 8/2007 Fushimi et al.
2007/0203448 A1 8/2007 Melker et al.
2007/0212428 A1 9/2007 Wittlin
2007/0212685 A1 9/2007 MacDonald et al.
2007/0218139 A1 9/2007 Smith et al.
2007/0224281 A1 9/2007 Park et al.
2007/0232648 A1 10/2007 Dahl et al.
2007/0243254 A1 10/2007 Edgren et al.
2007/0244130 A1 10/2007 Epple et al.
2007/0249583 A1 10/2007 Stein et al.
2007/0258938 A1 11/2007 Roy et al.
2007/0264358 A1 11/2007 Wittlin
2007/0269393 A1 11/2007 Wepfer
2007/0270453 A1 11/2007 Weinstein et al.
2007/0276001 A1 11/2007 Tung
2007/0287713 A1 12/2007 Cheng et al.
2008/0009533 A1 1/2008 Tino et al.
2008/0009534 A1 1/2008 Cheng et al.
2008/0014252 A1 1/2008 DelPrete
2008/0019978 A1 1/2008 Palani et al.

(56) **References Cited**

U.S. PATENT DOCUMENTS

2008/0058370 A1 3/2008 de Lera Ruiz et al.
2008/0064632 A1 3/2008 Amatruda et al.
2008/0078382 A1 4/2008 LeMahieu et al.
2008/0085306 A1 4/2008 Nangia et al.
2008/0118557 A1 5/2008 Liang et al.
2008/0131501 A1 6/2008 Liang et al.
2008/0171692 A1 7/2008 Hagmann et al.
2008/0194625 A1 8/2008 Sun et al.
2008/0221161 A1 9/2008 Pinkerton et al.
2008/0226715 A1 9/2008 Cha et al.
2008/0242593 A1 10/2008 Ewing et al.
2008/0242596 A1 10/2008 Chen et al.
2008/0242684 A1 10/2008 Dittrich
2008/0255093 A1 10/2008 Tam et al.
2008/0255194 A1 10/2008 Harbeson
2008/0292700 A1 11/2008 Nghiem et al.
2008/0293777 A1 11/2008 Erlanson et al.
2009/0004254 A1 1/2009 Maibach
2009/0018115 A1 1/2009 Gadde et al.
2009/0048232 A1 2/2009 Ciccocioppo
2009/0048235 A1 2/2009 Xia et al.
2009/0076053 A1 3/2009 Robbins
2009/0098200 A1 4/2009 Temtsin et al.
2009/0099143 A1 4/2009 Lagu et al.
2009/0105124 A1 4/2009 Smith et al.
2009/0117181 A1 5/2009 Uehara et al.
2009/0130216 A1 5/2009 Cartt et al.
2009/0137652 A1 5/2009 Twyman et al.
2009/0157662 A1 6/2009 Suffin et al.
2009/0176865 A1 7/2009 Breslav et al.
2009/0196890 A1 8/2009 Liang et al.
2009/0197886 A1 8/2009 Liotta et al.
2009/0215808 A1 8/2009 Yum et al.
2009/0232886 A1 9/2009 Sison
2009/0239942 A1 9/2009 Cloyd
2009/0247544 A1 10/2009 Morgan et al.
2009/0258844 A1 10/2009 Hochman
2009/0258902 A1 10/2009 Tung
2009/0270469 A1 10/2009 Gant et al.
2009/0304785 A1 12/2009 Najarian et al.
2009/0304789 A1 12/2009 Najarian et al.
2009/0306051 A1 12/2009 Meyerson et al.
2009/0311347 A1 12/2009 Oronsky et al.
2009/0325961 A1 12/2009 Duan et al.
2010/0056546 A1 3/2010 Gant et al.
2010/0063148 A1 3/2010 Christoph et al.
2010/0069341 A1 3/2010 Liotta et al.
2010/0074973 A1 3/2010 Gant et al.
2010/0076006 A1 3/2010 Johnson et al.
2010/0087422 A1 4/2010 Bird
2010/0105755 A1 4/2010 Gant et al.
2010/0105765 A1 4/2010 Najarian
2010/0113432 A1 5/2010 Gant et al.
2010/0113583 A1 5/2010 Aronne
2010/0119512 A1 5/2010 Feener et al.
2010/0119622 A1 5/2010 Gant et al.
2010/0119624 A1 5/2010 Gant et al.
2010/0120861 A1 5/2010 Gant et al.
2010/0124541 A1 5/2010 Gant et al.
2010/0125085 A1 5/2010 Gant et al.
2010/0129311 A1 5/2010 Gant
2010/0130528 A1 5/2010 Gant
2010/0130582 A1 5/2010 Gant et al.
2010/0130615 A1 5/2010 Gant
2010/0136004 A1 6/2010 Mei et al.
2010/0143507 A1 6/2010 Gant et al.
2010/0159033 A1 6/2010 Gant et al.
2010/0159034 A1 6/2010 Gant et al.
2010/0166887 A1 7/2010 Gant et al.
2010/0166889 A1 7/2010 Sanfilippo
2010/0167988 A1 7/2010 Gant et al.
2010/0167989 A1 7/2010 Gant
2010/0179129 A1 7/2010 Krishnan et al.
2010/0190752 A1 7/2010 Schiene et al.
2010/0197610 A1 8/2010 Lian et al.
2010/0215739 A1 8/2010 Najarian et al.
2010/0215774 A1 8/2010 Maibach
2010/0216805 A1 8/2010 Barlow et al.
2010/0234331 A1 9/2010 Xie et al.
2010/0240601 A1 9/2010 Piccariello et al.
2010/0247625 A1 9/2010 Geho et al.
2010/0266711 A1 10/2010 Gant et al.
2010/0279991 A1 11/2010 Liotta et al.
2010/0285001 A1 11/2010 Land et al.
2010/0286275 A1 11/2010 Zhang
2010/0286762 A1 11/2010 Gourdie et al.
2010/0292217 A1 11/2010 Belardinelli et al.
2010/0310599 A1 12/2010 Geho
2010/0317572 A1 12/2010 Mikkelsen et al.
2010/0317633 A1 12/2010 Xia et al.
2010/0317730 A1 12/2010 Shaya
2010/0317731 A1 12/2010 Shaya
2010/0331762 A1 12/2010 Wingeier et al.
2011/0008468 A1 1/2011 Haggarty et al.
2011/0014296 A1 1/2011 Chen et al.
2011/0015663 A1 1/2011 Aronne
2011/0021564 A1 1/2011 Sanfilippo
2011/0053914 A1 3/2011 Schiene et al.
2011/0059170 A1 3/2011 McKinney et al.
2011/0065628 A1 3/2011 Johnson et al.
2011/0081426 A1 4/2011 Rao et al.
2011/0082407 A1 4/2011 Aronne
2011/0097326 A1 4/2011 Luehrsen
2011/0104315 A1 5/2011 Sun et al.
2011/0117070 A1 5/2011 Aurora et al.
2011/0117214 A1 5/2011 Newbold et al.
2011/0142914 A1 6/2011 Persaud et al.
2011/0178148 A1 7/2011 Xia et al.
2011/0195096 A1 8/2011 Kindler et al.
2011/0206780 A1 8/2011 Gant et al.
2011/0206782 A1 8/2011 Zhang
2011/0207661 A1 8/2011 Chen et al.
2011/0207718 A1 8/2011 Bird
2011/0212171 A1 9/2011 Venkatesh et al.
2011/0212944 A1 9/2011 Liu et al.
2011/0224196 A1 9/2011 Wilson et al.
2011/0230461 A1 9/2011 Bhattacharya et al.
2011/0236485 A1 9/2011 Berner et al.
2011/0244057 A1 10/2011 Ehrenberg
2011/0245208 A1 10/2011 Diatchenko et al.
2011/0245287 A1 10/2011 Holaday et al.
2011/0251248 A1 10/2011 Lin et al.
2011/0257260 A1 10/2011 Rao et al.
2011/0262535 A1 10/2011 Najarian et al.
2011/0281795 A1 11/2011 Lin et al.
2011/0287099 A1 11/2011 Liang et al.
2011/0287103 A1 11/2011 Liang et al.
2011/0288079 A1 11/2011 Kiel et al.
2011/0294787 A1 12/2011 Wenzel et al.
2011/0301082 A1 12/2011 Lin et al.
2011/0306624 A1 12/2011 Lin et al.
2011/0312911 A1 12/2011 Kats-Kagan et al.
2011/0319388 A1 12/2011 De Almeida et al.
2012/0003312 A1 1/2012 Nutalapati et al.
2012/0020954 A1 1/2012 Achiron et al.
2012/0035105 A1 2/2012 Geho et al.
2012/0039881 A1 2/2012 Mei et al.
2012/0082659 A1 4/2012 Land et al.
2012/0109253 A1 5/2012 Wingeier et al.
2012/0114670 A1 5/2012 Land et al.
2012/0115849 A1 5/2012 Demopulos et al.
2012/0128683 A1 5/2012 Shantha
2012/0148689 A1 6/2012 Maibach
2012/0196881 A1 8/2012 Najarian et al.
2012/0238554 A1 9/2012 Cowen
2012/0252833 A1 10/2012 Wertz et al.

FOREIGN PATENT DOCUMENTS

EP 1 627 881 B1 10/2006
EP 1 731 524 A1 12/2006
EP 1 775 303 A1 4/2007
EP 1 977 736 A1 10/2008
EP 1 499 300 B1 3/2009

(56) **References Cited**

FOREIGN PATENT DOCUMENTS

WO	WO 98/00124	A1	1/1998
WO	WO 98/00129	A2	1/1998
WO	WO 98/15270	A1	4/1998
WO	WO 99/44581	A2	9/1999
WO	WO 00/01376	A2	1/2000
WO	WO 00/23059	A2	4/2000
WO	WO 00/32183	A1	6/2000
WO	WO 00/42995	A2	7/2000
WO	WO 00/44374	A1	8/2000
WO	WO 00/61140	A1	10/2000
WO	WO 00/06096	A2	11/2000
WO	WO 00/66108	A2	11/2000
WO	WO 01/27107	A2	4/2001
WO	WO 01/89445	A1	11/2001
WO	WO 01/96311	A2	12/2001
WO	WO 01/96347	A1	12/2001
WO	WO 02/00221	A1	1/2002
WO	WO 02/053187	A2	7/2002
WO	WO 02/078730	A2	10/2002
WO	WO 02/083128	A1	10/2002
WO	WO 02/087590	A1	11/2002
WO	WO 02/096357	A2	12/2002
WO	WO 02/098418	A1	12/2002
WO	WO 03/020289	A1	3/2003
WO	WO 03/020737	A1	3/2003
WO	WO 03/026676	A1	4/2003
WO	WO 03/037379	A1	5/2003
WO	WO 03/039563	A1	5/2003
WO	WO 03/041697	A1	5/2003
WO	WO 03/070738	A2	8/2003
WO	WO 03/072138	A1	9/2003
WO	WO 03/080072	A1	10/2003
WO	WO 03/090723	A1	11/2003
WO	WO 03/097038	A1	11/2003
WO	WO 03/097046	A1	11/2003
WO	WO 03/097656	A2	11/2003
WO	WO 03/099273	A1	12/2003
WO	WO 03/101380	A2	12/2003
WO	WO 2004/002447	A2	1/2004
WO	WO 2004/009015	A2	1/2004
WO	WO 2004/009017	A2	1/2004
WO	WO 2004/010970	A1	2/2004
WO	WO 2004/026299	A1	4/2004
WO	WO 2004/030637	A2	4/2004
WO	WO 2004/054547	A1	7/2004
WO	WO 2004/054965	A1	7/2004
WO	WO 2004/058222	A1	7/2004
WO	WO 2004/078161	A1	9/2004
WO	WO 2004/078163	A2	9/2004
WO	WO 2004/078769	A1	9/2004
WO	WO 2004/089965	A2	10/2004
WO	WO 2004/105682	A2	12/2004
WO	WO 2004/110385	A2	12/2004
WO	WO 2004/111015	A1	12/2004
WO	WO 2005/000807	A2	1/2005
WO	WO 2005/013894	A2	2/2005
WO	WO 2005/016306	A2	2/2005
WO	WO 2005/020957	A2	3/2005
WO	WO 2005/020959	A2	3/2005
WO	WO 2005/020961	A1	3/2005
WO	WO 2005/030758	A1	4/2005
WO	WO 2005/048979	A2	6/2005
WO	WO 2005/048981	A1	6/2005
WO	WO 2005/048990	A2	6/2005
WO	WO 2005/049043	A1	6/2005
WO	WO 2005/051358	A1	6/2005
WO	WO 2005/051386	A1	6/2005
WO	WO 2005/063248	A1	7/2005
WO	WO 2005/063297	A2	7/2005
WO	WO 2005/065648	A2	7/2005
WO	WO 2005/070207	A1	8/2005
WO	WO 2005/070461	A2	8/2005
WO	WO 2005/072729	A1	8/2005
WO	WO 2005/072732	A1	8/2005
WO	WO 2005/073221	A1	8/2005
WO	WO 2005/077925	A1	8/2005
WO	WO 2005/079748	A2	9/2005
WO	WO 2005/097125	A2	10/2005
WO	WO 2005/099674	A1	10/2005
WO	WO 2005/110405	A1	11/2005
WO	WO 2005/113506	A1	12/2005
WO	WO 2005/113519	A1	12/2005
WO	WO 2006/007323	A2	1/2006
WO	WO 2006/009403	A1	1/2006
WO	WO 2006/014484	A2	2/2006
WO	WO 2006/015930	A1	2/2006
WO	WO 2006/017238	A1	2/2006
WO	WO 2006/017341	A2	2/2006
WO	WO 2006/017524	A2	2/2006
WO	WO 2006/017537	A1	2/2006
WO	WO 2006/019978	A2	2/2006
WO	WO 2006/031491	A2	3/2006
WO	WO 2006/031610	A2	3/2006
WO	WO 2006/031676	A2	3/2006
WO	WO 2006/044472	A1	4/2006
WO	WO 2006/047204	A1	5/2006
WO	WO 2006/047450	A2	5/2006
WO	WO 2006/049933	A2	5/2006
WO	WO 2006/067494	A1	6/2006
WO	WO 2006/076632	A1	7/2006
WO	WO 2006/076633	A1	7/2006
WO	WO 2006/076796	A1	7/2006
WO	WO 2006/077492	A1	7/2006
WO	WO 2006/082245	A1	8/2006
WO	WO 2006/084176	A2	8/2006
WO	WO 2006/088305	A1	8/2006
WO	WO 2006/092691	A1	9/2006
WO	WO 2006/097946	A1	9/2006
WO	WO 2006/101950	A2	9/2006
WO	WO 2006/102029	A2	9/2006
WO	WO 2006/107903	A2	10/2006
WO	WO 2006/113095	A2	10/2006
WO	WO 2006/121363	A1	11/2006
WO	WO 2006/127748	A1	11/2006
WO	WO 2006/130522	A2	12/2006
WO	WO 2007/002872	A2	1/2007
WO	WO 2007/008551	A2	1/2007
WO	WO 2007/008562	A2	1/2007
WO	WO 2007/014929	A1	2/2007
WO	WO 2007/016108	A1	2/2007
WO	WO 2007/017764	A2	2/2007
WO	WO 2007/022255	A2	2/2007
WO	WO 2007/026224	A2	3/2007
WO	WO 2007/032720	A1	3/2007
WO	WO 2007/035425	A2	3/2007
WO	WO 2007/038610	A2	4/2007
WO	WO 2007/047351	A2	4/2007
WO	WO 2007/048027	A2	4/2007
WO	WO 2007/056366	A2	5/2007
WO	WO 2007/056496	A1	5/2007
WO	WO 2007/056497	A1	5/2007
WO	WO 2007/063418	A2	6/2007
WO	WO 2007/067341	A2	6/2007
WO	WO 2007/075555	A2	7/2007
WO	WO 2007/087154	A2	8/2007
WO	WO 2007/087204	A2	8/2007
WO	WO 2007/087448	A1	8/2007
WO	WO 2007/089318	A2	8/2007
WO	WO 2007/089557	A2	8/2007
WO	WO 2007/089667	A1	8/2007
WO	WO 2007/094825	A2	8/2007
WO	WO 2007/099388	A1	9/2007
WO	WO 2007/100902	A2	9/2007
WO	WO 2007/100905	A2	9/2007
WO	WO 2007/106862	A2	9/2007
WO	WO 2007/108009	A1	9/2007
WO	WO 2007/115997	A2	10/2007
WO	WO 2007/117466	A2	10/2007
WO	WO 2007/117549	A2	10/2007
WO	WO 2007/119178	A2	10/2007
WO	WO 2007/112581	A1	11/2007
WO	WO 2007/128349	A1	11/2007
WO	WO 2007/130848	A2	11/2007
WO	WO 2007/137164	A2	11/2007

(56) **References Cited**

FOREIGN PATENT DOCUMENTS

WO	WO 2007/137167	A2	11/2007
WO	WO 2007/140191	A2	12/2007
WO	WO 2007/143422	A2	12/2007
WO	WO 2008/002816	A1	1/2008
WO	WO 2008/002817	A1	1/2008
WO	WO 2008/002818	A1	1/2008
WO	WO 2008/002820	A2	1/2008
WO	WO 2008/010231	A2	1/2008
WO	WO 2008/027557	A2	3/2008
WO	WO 2008/036798	A2	3/2008
WO	WO 2008/061226	A2	5/2008
WO	WO 2008/070670	A2	6/2008
WO	WO 2008/061226	A3	7/2008
WO	WO 2008/088820	A2	7/2008
WO	WO 2008/089521	A1	7/2008
WO	WO 2008/091692	A2	7/2008
WO	WO 2008/091934	A2	7/2008
WO	WO 2008/095086	A2	8/2008
WO	WO 2008/095253	A1	8/2008
WO	WO 2008/097976	A1	8/2008
WO	WO 2008/098195	A2	8/2008
WO	WO 2008/098195	A3	9/2008
WO	WO 2008/106659	A2	9/2008
WO	WO 2008/109343	A1	9/2008
WO	WO 2008/115705	A2	9/2008
WO	WO 2008/115797	A1	9/2008
WO	WO 2008/106659	A3	10/2008
WO	WO 2008/121882	A1	10/2008
WO	WO 2008/122014	A1	10/2008
WO	WO 2008/128126	A1	10/2008
WO	WO 2008/128166	A1	10/2008
WO	WO 2008/091692	A3	11/2008
WO	WO 2008/095086	A3	11/2008
WO	WO 2008/088820	A3	12/2008
WO	WO 2008/148064	A1	12/2008
WO	WO 2008/153632	A2	12/2008
WO	WO 2008/156550	A2	12/2008
WO	WO 2008/115705	A3	1/2009
WO	WO 2008/128126	A8	1/2009
WO	WO 2009/015236	A1	1/2009
WO	WO 2009/018132	A2	2/2009
WO	WO 2009/018326	A2	2/2009
WO	WO 2009/021129	A1	2/2009
WO	WO 2009/023292	A1	2/2009
WO	WO 2009/023653	A2	2/2009
WO	WO 2009/026241	A1	2/2009
WO	WO 2009/018326	A3	3/2009
WO	WO 2009/029308	A1	3/2009
WO	WO 2009/035473	A2	3/2009
WO	WO 2009/040818	A1	4/2009
WO	WO 2009/042960	A1	4/2009
WO	WO 2009/045443	A2	4/2009
WO	WO 2009/054544	A1	4/2009
WO	WO 2009/018132	A3	5/2009
WO	WO 2009/018132	A9	6/2009
WO	WO 2009/073843	A1	6/2009
WO	WO 2008/153632	A3	7/2009
WO	WO 2008/156550	A3	7/2009
WO	WO 2009/080691	A2	7/2009
WO	WO 2009/092049	A1	7/2009
WO	WO 2009/080691	A3	8/2009
WO	WO 2009/108837	A2	9/2009
WO	WO 2009/126931	A2	10/2009
WO	WO 2009/131692	A1	10/2009
WO	WO 2009/132119	A2	10/2009
WO	WO 2009/133128	A1	11/2009
WO	WO 2009/133141	A2	11/2009
WO	WO 2009/133142	A1	11/2009
WO	WO 2008/091934	A3	12/2009
WO	WO 2009/035473	A3	12/2009
WO	WO 2009/045443	A3	12/2009
WO	WO 2009/108837	A3	12/2009
WO	WO 2009/133141	A3	12/2009
WO	WO 2009/152189	A1	12/2009
WO	WO 2009/152190	A1	12/2009
WO	WO 2010/002869	A1	1/2010
WO	WO 2010/005507	A1	1/2010
WO	WO 2010/009335	A1	1/2010
WO	WO 2009/132119	A3	2/2010
WO	WO 2010/013240	A1	2/2010
WO	WO 2010/015029	A1	2/2010
WO	WO 2010/015567	A2	2/2010
WO	WO 2009/126931	A3	3/2010
WO	WO 2010/025931	A2	3/2010
WO	WO 2010/030722	A1	3/2010
WO	WO 2010/036977	A2	4/2010
WO	WO 2010/044736	A1	4/2010
WO	WO 2010/045416	A2	4/2010
WO	WO 2010/048358	A2	4/2010
WO	WO 2009/040818	A9	5/2010
WO	WO 2010/057104	A2	5/2010
WO	WO 2010/059639	A2	5/2010
WO	WO 2010/060037	A2	5/2010
WO	WO 2010/060041	A2	5/2010
WO	WO 2010/060070	A2	5/2010
WO	WO 2010/071750	A1	6/2010
WO	WO 2010/075086	A2	7/2010
WO	WO 2010/080976	A1	7/2010
WO	WO 2010/088061	A1	8/2010
WO	WO 2010/093535	A1	8/2010
WO	WO 2010/098888	A1	9/2010
WO	WO 2010/098948	A1	9/2010
WO	WO 2010/098994	A1	9/2010
WO	WO 2010/099217	A1	9/2010
WO	WO 2010/113096	A1	10/2010
WO	WO 2010/118291	A2	10/2010
WO	WO 2010/132696	A1	11/2010
WO	WO 2010/147830	A2	12/2010
WO	WO 2011/008298	A2	1/2011
WO	WO 2011/009115	A2	1/2011
WO	WO 2011/011420	A2	1/2011
WO	WO 2011/023392	A1	3/2011
WO	WO 2011/038210	A2	3/2011
WO	WO 2011/041632	A2	4/2011
WO	WO 2011/047383	A1	4/2011
WO	WO 2011/050008	A2	4/2011
WO	WO 2011/054759	A1	5/2011
WO	WO 2011/060363	A2	5/2011
WO	WO 2011/075688	A1	6/2011
WO	WO 2011/085181	A1	7/2011
WO	WO 2011/085256	A2	7/2011
WO	WO 2011/101866	A2	8/2011
WO	WO 2011/107749	A2	9/2011
WO	WO 2011/107750	A2	9/2011
WO	WO 2011/107755	A2	9/2011
WO	WO 2011/107855	A2	9/2011
WO	WO 2011/114271	A1	9/2011
WO	WO 2011/119953	A1	9/2011
WO	WO 2011/120044	A1	9/2011
WO	WO 2011/101866	A3	10/2011
WO	WO 2011/123610	A2	10/2011
WO	WO 2011/126910	A2	10/2011
WO	WO 2011/138421	A1	11/2011
WO	WO 2011/143721	A1	11/2011
WO	WO 2011/149757	A1	12/2011
WO	WO 2011/163612	A1	12/2011
WO	WO 2011/163619	A1	12/2011
WO	WO 2012/022730	A1	2/2012
WO	WO 2012/033874	A1	3/2012
WO	WO 2012/056372	A1	5/2012
WO	WO 2012/064667	A2	5/2012
WO	WO 2012/074561	A2	6/2012
WO	WO 2012/098245	A1	7/2012
WO	WO 2012/100248	A1	7/2012
WO	WO 2012/100347	A1	8/2012
WO	WO 2012/103520	A1	8/2012

OTHER PUBLICATIONS

Bialer, "Extended-release formulations for the treatment of epilepsy" Sep. 18, 2007, *CNS Drugs* 21(9):765-74.

Bourgeois, "Important pharmacokinetic properties of antiepileptic drugs," 1995 *Epilepsia* 36(Suppl 5):S1-7.

(56) **References Cited**

OTHER PUBLICATIONS

Cramer et al., "The relationship between poor medication compliance and seizures," 2002 *Epilepsy Behav*. 3:38-42.

Cydex website. Available online [retrieved on Apr. 21, 2008]. Retrieved from the Internet: <http://www.cydexinc.com/captisol.asp>; 1 page.

Dib, "Focus on topiramate in neuropathic pain" *Current Medical Research and Opinion*, Dec. 1, 2004, 20 (12) p. 1857-1861.

Doose et al., "Single-dose pharmacokinetics and effect of food on the bioavailability of topiramate, a novel antiepileptic drug," 1996 *J Clin Pharmacol*. 36:884-91.

Food and Drug Administration, "Guidance for Industry. Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations," U.S. Department of Health and Human Services, Center for Drug Evaluation and Research (CDER). Sep. 1997.

Food and Drug Administration, "Guidance for industry: Food-effect bioavailability and fed bioequivalence studies," Dec. 2002.

Food and Drug Administration, "Guidance for industry: Bioavailability and bioequivalence studies for orally administered drug products—general considerations," Mar. 2003.

Frohoff-Hulsmann et al., "Aqueous ethyl cellulose dispersions containing plasticizers of difference water solubility and hydroxypropyl methylcellulose as coating material for diffusions pellets I. Drug release rates from coated pellets," 1999 *Int. J. Pharmaceutics* 177:69-82.

Garnett, "Clinical pharmacology of topiramate: a review," 2000 *Epilepsia* 41(Supp 1):S61-5.

Halvorsen et al., "Pharmacokinetic Equivalence between Immediate-Release Topiramate and USL255, A Novel Extended-Release Formulation of Topiramate," poster presented at the *64th Annual Meeting of the American Epilepsy Society*; San Antonio, Texas: Dec. 3-7, 2010.

Halvorsen et al., "Extended-Release Topiramate (USL255) Exhibits Linear Dose-Proportional Pharmacokinetic Characteristics," poster presented at the *65th Annual Meeting of the American Epilepsy Society*; Baltimore, MD: Dec. 2-6, 2011.

Halvorsen et al., "Establishing Maximum Tolerated Dose and Dose-Proportionality in Extended-Release Topiramate (USL255)," poster presented at the *66th Annual Meeting of the American Epilepsy Society*; San Diego, CA: Nov. 30-Dec. 4, 2012.

Halvorsen et al., "Extended-Release Topiramate (USL255) Exhibits Linear Dose-Proportional Pharmacokinetic Characteristics," Conference Abstract No. P06.128. *62nd Annual Meeting of the American Academy of Neurology* (*AAN*); New Orleans, LA: Apr. 22-27, 2012. Published online: *Neurology* 2012;78(suppl 1): P06.128. [retrieved on May 6, 2013]. Retrieved from the Internet: <http ://www.neurology.org/cgi/content/meeting_abstract/78/1_MeetingAbstracts/P06.128>; 2 pages.

Hirst et al., "Gastrointestinal performance of the Microtrol extended release drug delivery technology," *Proceed. Int'l Symp. Control. Rel. Bioact. Mater*., 26 (Revised Jul. 1999) Controlled Release Society, Inc.

"Johnson & Johnson to Acquire TransForm Pharmaceuticals" Press Release dated Mar. 9, 2005. Available on the J&J website [retrieved on Apr. 22, 2008]. Retrieved from the Internet: <http://www.investor.jnj.com/releasedetail.cfm?ReleaseID=157580&textOnly=false>; 2 pages.

Lambrecht et al., "Development and Optimization of Extended-Release Formulations of Topiramate," poster presented at the *64th Annual Meeting of the American Epilepsy Society*; San Antonio, Texas: Dec. 3-7, 2010.

Lambrecht et al., "Development and optimization of extended-release formulations of topiramate," Abstract No. 1.116 presented at the *63rd Annual Meeting of the American Academy of Neurology* (*AAN*); Honolulu, HI: Apr. 9-16, 2011.

Lambrecht et al., "Pharmacokinetic Equivalence between Immediate-Release and Extended-Release Topiramate," Poster Abstract No. M710 presented at the *136th Annual Meeting of the American Neurological Association* Sep. 25-27, 2011: San Diego, CA. Published in Oct. 2011 *Ann Neurol*. 70 (Suppl. 15):593-S102.

Lambrecht et al., "Steady-State Pharmacokinetics of USL255, an Extended-Release Formulation of Topiramate," poster presented at the *65th Annual Meeting of the American Epilepsy Society*; Baltimore, MD: Dec. 2-6, 2011.

Lambrecht et al., "Comparative pharmacokinetic analysis of USL255, a new once-daily extended-release formulation of topiramate," 2011 *Epilepsia* 52(10):1877-1883. Available online on Jul. 19, 2011.

Nahata et al., "Topiramate stability in two oral suspensions stored in plastic prescription bottles at two temperatures" Poster abstract No. P-77R; presented as the *46th American Society of Health-System Pharmacists (ASHP) Midyear Clinical Meeting*, Dec. 4-8, 2001: New Orleans, LA. v36.

Rosenstock et al., "A randomized, double-blind, placebo-controlled, multicenter study to assess the efficacy and safety of topiramate controlled release in the treatment of obese type 2 diabetic patients" *Diabetes Care*, Jun. 2007, 30 (6) p. 148-146.

Shank et al., "Plasma and whole blood pharmacokinetics of topiramate: the role of carbonic anhydrase," Feb. 2005 *Epilepsy Res*. 63(2-3):103-112.

Smith et al., "Confidence interval criteria for assessment of dose proportionality," Oct. 2000 *Pharm Res*. 17(10):1278-1283.

Styslo-Zalasik et al., "Determination of topiramate and its degradation product in liquid oral solutions by high performance liquid chromatography with a chemiluminescent nitrogen detector," *J. Pharm. Biomed. Anal*., 2005, 37(3):529-34.

Syed et al., "Extended-release lamotrigine in the treatment of patients with epilepsy," 2010 *Expert Opin Pharmacother*. 11:1579-85.

Todd et al., "The Effect of Food on the Bioavailablity of USL255 A Novel Extended-Release Formulation of Topiramate," poster presented at the *64th Annual Meeting of the American Epilepsy Society*; San Antonio, Texas: Dec. 3-7, 2010.

Tonstad et al., "Efficacy and safety of topiramate in the treatment of obese subjects with essential hypertension," Jul. 15, 2005 *American Journal of Cardiology* 96(2):243-51.

Topamax [Prescribing Information]. Titusville, NJ: Janssen Pharmaceuticals, revised 2012. 46 pages.

Treiman, "Management of refractory complex partial seizures: current state of the art," May 25, 2010 *Neuropsychiatr Dis Treat*. 6:297-308.

World Health Organization. Epilepsy Fact Sheet; last updated Oct. 2012. http://www.who.int/mediacentre/factsheets/fs999/en/index.html. Accessed May 6, 2013.

Yin et al., "Optimizing first-time-in-human trial design for studying dose proportionality," 2001 *Drug Information Journal*. 35:1065-1078.

International Search Report and Written Opinion mailed Apr. 16, 2014 in connection with International Patent Application No. PCT/US2014/010284, filed Jan. 6, 2014; 29 pages.

* cited by examiner

EXTENDED-RELEASE TOPIRAMATE CAPSULES

CONTINUING APPLICATION DATA

This application is a continuation of U.S. patent application Ser. No. 14/157,646, filed Jan. 17, 2014, which is a continuation of U.S. patent application Ser. No. 13/847,042, filed Mar. 19, 2013, now issued as U.S. Pat. No. 8,652,527.

BACKGROUND

The pharmaceutical industry employs a variety of dosage formulations for orally administering medicinal agents to patients. Typical formulations for oral administration include liquid solutions, emulsions, or suspensions, as well as solid forms such as capsules or tablets (as used herein, the term "tablet" means any shaped and compressed solid dosage form, including caplets).

Efficacy of a drug product often depends on patient compliance with a dosing schedule. Therefore, one per day, extended-release, dosages have better efficacy over the long term than multidose regimens.

SUMMARY

The present disclosure provides solid dosage formulations of topiramate [2,3:4,5-bis-O-(1-methylethylidene)-β-D-fructopyranose sulfamate], particularly capsules, containers including such capsules, and methods of dosing.

In one embodiment, the present disclosure provides an extended-release formulation that is dosed once-per-day, in the form of a capsule.

In one embodiment, the present disclosure provides an extended-release topiramate capsule that includes a capsule shell and a single population of coated particles contained within the capsule shell, wherein each coated particle includes a core and a coating thereon. In certain embodiments, the particles, whether coated or uncoated, are spherical.

Each particle core includes a homogeneous mixture including topiramate throughout the core. In certain embodiments, each particle core also includes a filler and/or a binder (preferably, both a filler and a binder) in the homogeneous mixture.

The coating includes a release controlling agent. In certain embodiments, the coating also includes a pore former and/or a plasticizer.

In one embodiment, an extended-release topiramate capsule is provided that includes: a capsule shell containing a single population of coated particles; wherein each coated particle includes a core and a coating thereon; wherein each particle core includes a homogeneous mixture throughout its core, the mixture including: 40 wt-% to 50 wt-% of topiramate, based on the total weight of an uncoated particle core; 45 wt-% to 55 wt-% of one or more filler(s), based on the total weight of an uncoated particle core; and 3 wt-% to 7 wt-% of one or more binder(s), based on the total weight of an uncoated particle core; wherein the coating includes: 55 wt-% to 65 wt-% of one or more release control agent(s), based on the total weight of the coating; 20 wt-% to 25 wt-% of one or more pore former(s), based on the total weight of the coating; and 10 wt-% to 20 wt-% of one or more plasticizer(s), based on the total weight of the coating; wherein the particles are coated in an amount sufficient to provide a (coating) weight gain of 8% to 14%.

As used herein, the terms "topiramate active agent" and "active agent of topiramate" and "topiramate" are synonymous and are used interchangeably throughout the specification to refer to the compound 2,3:4,5-bis-O-(1-methylethylidene)-β-D-fructopyranose sulfamate. Included within these terms are also pharmaceutically acceptable salts thereof as well as polymorphs, solvates, hydrates, dehydrates, co-crystals, anhydrous, and amorphous forms thereof.

The term "extended-release" means release of an active agent over a period of time, which is much longer than the release from an immediate release formulation, which usually releases more than 80% of the active agent in 60 minutes or less.

The term "therapeutically effective amount" as used herein means that amount of active compound that elicits the biological or medicinal response in a tissue, system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes alleviation and/or prevention of the symptoms of the condition being treated.

The terms "comprises" and variations thereof do not have a limiting meaning where these terms appear in the description and claims. Such terms will be understood to imply the inclusion of a stated step or element or group of steps or elements but not the exclusion of any other step or element or group of steps or elements. By "consisting of" is meant including, and limited to, whatever follows the phrase "consisting of." Thus, the phrase "consisting of" indicates that the listed elements are required or mandatory, and that no other elements may be present. By "consisting essentially of" is meant including any elements listed after the phrase, and limited to other elements that do not interfere with or contribute to the activity or action specified in the disclosure for the listed elements. Thus, the phrase "consisting essentially of" indicates that the listed elements are required or mandatory, but that other elements are optional and may or may not be present depending upon whether or not they materially affect the activity or action of the listed elements.

The words "preferred" and "preferably" refer to embodiments of the disclosure that may afford certain benefits, under certain circumstances. However, other embodiments may also be preferred, under the same or other circumstances. Furthermore, the recitation of one or more preferred embodiments does not imply that other embodiments are not useful, and is not intended to exclude other embodiments from the scope of the disclosure.

As used herein, "a," "an," "the," "at least one," and "one or more" are used interchangeably. Thus, for example, a particle core that comprises "a" binder can be interpreted to mean that the particle core includes "one or more" binders. Similarly, a coating comprising "a" pore former can be interpreted to mean that the composition includes "one or more" pore formers.

As used herein, the term "or" is generally employed in its usual sense including "and/or" unless the content clearly dictates otherwise.

The term "and/or" means one or all of the listed elements or a combination of any two or more of the listed elements (e.g., preventing and/or treating an affliction means preventing, treating, or both preventing and treating an affliction).

Also herein, all numbers are assumed to be modified by the term "about" and preferably by the term "exactly." As used herein in connection with a measured quantity, the term "about" refers to that variation in the measured quantity as would be expected by the skilled artisan making the measure-

ment and exercising a level of care commensurate with the objective of the measurement and the precision of the measuring equipment used.

Also herein, the recitations of numerical ranges by endpoints include all numbers subsumed within that range as well as the endpoints (e.g., 1 to 5 includes 1, 1.5, 2, 2.75, 3, 3.80, 4, 5, etc.). Herein, "up to" a number (e.g., up to 50) includes the number (e.g., 50).

The above summary of the present disclosure is not intended to describe each disclosed embodiment or every implementation of the present disclosure. The description that follows more particularly exemplifies illustrative embodiments. In several places throughout the application, guidance is provided through lists of examples, which examples can be used in various combinations. In each instance, the recited list serves only as a representative group and should not be interpreted as an exclusive list.

DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

The present disclosure provides solid dosage formulations of topiramate [2,3:4,5-bis-O-(1-methylethylidene)-β-D-fructopyranose sulfamate]. Such solid dosage formulations are extended-release once-per-day dosage capsules (i.e., designed for administration once per day).

In one embodiment, the present disclosure provides an extended-release topiramate capsule that includes a capsule shell and a single population of coated particles contained within the capsule shell. In this context, "a single population" means that all the particles in one capsule are the same (within reasonable manufacturing variability) with respect to composition. In this context, "same" means the particles in one capsule are made in a single batch process or in multiple batches using identical processes.

The use of a single population of particles in any one capsule provides significant advantages from a manufacturing (e.g., quality and cost) perspective. For example, different populations of particles (e.g., beads), having different compositions, do not need to be manufactured for one product.

Furthermore, in certain embodiments, the capsules of the present disclosure do not include an immediate release component in any significant amount. Typically, capsules of the present invention are free of an immediate-release component.

Each coated particle includes a core and a coating thereon. In certain embodiments, the particles, whether coated or uncoated, are spherical, as defined in greater detail below.

Each particle core includes a homogeneous mixture including topiramate throughout the core. In certain embodiments, each particle core also includes a filler and/or a binder (preferably, both a filler and a binder) in the homogeneous mixture.

The coating on each core includes a release controlling agent. In certain embodiments, the coating also includes a pore former and/or a plasticizer.

In one embodiment, the present disclosure provides a solid dosage formulation that includes a capsule including core particles with a coating thereon. The core particles include the active agent. The core particles can also include a filler and/or a binder (preferably, both a filler and a binder). The coating includes a release-controlling agent. The coating can also include a pore former and/or a plasticizer.

In certain embodiments, the particles, whether coated or uncoated, are spherical. In this context, the term "spherical" refers to particles that are generally rounded by visual inspection. They may or may not be perfectly spherical. A representative population of spherical particles (i.e., beads) typically has an average sphericity of at least 0.7. In certain embodiments, the average sphericity of a representative population of particles is at least 0.75, and in certain embodiments at least 0.8. A preferred sphericity is 0.8. Sphericity can be determined by use of a digital microscope and a two-dimensional image analysis software (e.g., such as that by Soft Imaging System GmbH, version 5.0 Build 1054).

In certain embodiments, the particle size (which is typically the diameter of a spherical particle) of the coated particles is at least 500 μm (microns). In certain embodiments, the particle size of the coated particles is up to 1300 μm. In certain embodiments, the majority of the particles in a capsule are typically in a range of 700 μm to 1000 μm.

The rate of particle dissolution is typically dependent on the coating weight, which can be adjusted during manufacture. In certain embodiments, the particles are coated in an amount sufficient to provide a weight gain of at least 2%, or at least 4%, or at least 6%, or at least 8%, or at least 9%, or at least 10%. In certain embodiments, the particles are coated in an amount sufficient to provide a weight gain of up to 30%, or up to 25%, or up to 20%, or up to 15%, or up to 12%. Preferably, the particles are coated in an amount sufficient to provide a weight gain of 10% to 12%. In certain embodiments, the particles are coated in an amount sufficient to provide a weight gain of 8% to 14%.

In this context, "weight gain" is defined as the theoretical weight gain of a population of particles as a result of coating, assuming 100% coating efficiency. Thus, "weight gain" refers to coating weight gain. As an example, 100 grams of uncoated particles (e.g., beads) coated to a theoretical weight gain of 8% means that an amount of coating solution having 8 grams (g) of non-volatile components, e.g., release controlling agent, pore former, and plasticizer, was applied to the uncoated beads in a coating step, but there may be some losses in the manufacturing process.

Suitable active agents within the particle core include topiramate (2,3:4,5-bis-O-(1-methylethylidene)-β-D-fructopyranose sulfamate). "Topiramate" refers to 2,3:4,5-bis-O-(1-methylethylidene)-β-D-fructopyranose sulfamate as well as pharmaceutically acceptable salts of topiramate, including without limitation, topiramate sodium, topiramate lithium, topiramate potassium, as well as polymorphs, solvates, hydrates, dehydrates, co-crystals, anhydrous, and amorphous forms thereof. Topiramate can be purchased from commercial sources. It is presently available for marketing as an immediate-release tablet product (as TOPAMAX) for certain seizure indications and migraine prophylaxis.

An amount of topiramate active agent is included within a capsule in an amount sufficient to deliver the desired dose. Alternatively stated, a therapeutically effective amount of topiramate is included within a capsule. A capsule can include a topiramate active agent in an amount of at least 10 weight percent (wt-% or % w/w), or at least 25 wt-%, or at least 35 wt-%, or at least 40 wt-%, or at least 44 wt-%, based on the total weight of an uncoated particle core. A capsule can include a topiramate active agent in an amount of up to 80 wt-%, or up to 50 wt-%, or up to 46 wt-%, based on the total weight of an uncoated particle core. In certain embodiments, the particle cores of the capsules of the present disclosure include 40 wt-% to 50 wt-% topiramate active agent, based on the total weight of an uncoated particle core. In certain embodiments, the particle cores of the capsules of the present disclosure include 44 wt-% to 46 wt-% topiramate active agent, based on the total weight of an uncoated particle core.

The active agent can be homogeneously mixed within a particle core that includes one or more fillers and/or binders.

One or more stabilizers can also be included in the particle core. Inclusion of a stabilizer may help maintain the potency of topiramate over time.

Herein, for any component specified, if there are multiple grades (e.g., molecular weights) of such component, recitation of the component implies any or all of such variations.

Suitable fillers for use in the particle cores include, but are not limited to, microcrystalline cellulose, dibasic calcium phosphate, lactose, tribasic calcium phosphate, mannitol, other suitable carbohydrates (e.g., other sugars or starches). Combinations of fillers can be used if desired. Preferably, microcrystalline cellulose is used as a filler (such as that available from JRS Pharma under the trade designation EMCOCEL 90M).

One or more fillers can be used in an amount of at least 10 wt-%, or at least 25 wt-%, or at least 45 wt-%, or at least 48 wt-%, based on the total weight of the uncoated particle core. One or more fillers can be used in an amount of up to 85 wt-%, or up to 75 wt-%, or up to 55 wt-%, or up to 52 wt-%, based on the total weight of the uncoated particle core. In certain embodiments, the particle cores of the capsules of the present disclosure include 45 wt-% to 55 wt-% filler(s), based on the total weight of an uncoated particle core. In certain embodiments, the particle cores of the capsules of the present disclosure include 48 wt-% to 52 wt-% filler(s), based on the total weight of an uncoated particle core.

Suitable binders for use in the particle core include, but are not limited to, hydroxypropyl methylcellulose (i.e., hypromellose or "HPMC"), methylcellulose, carboxymethylcellulose, sodium carboxymethylcellulose, hydroxypropyl cellulose, hydroxyethylcellulose, polyvinyl pyrrolidine (i.e., povidone), starch (e.g., pregelatinized starch), and natural gum (e.g., acacia gum, sodium alginate, guar gum, xanthan gum). Combinations of binders can be used if desired. Preferably, hydroxypropyl methylcellulose (hypromellose 2910) is used as a binder (such as that available from The Dow Chemical Company under the trade designation METHOCEL E5 Premium).

One or more binders can be used in an amount of at least 1 wt-%, or at least 2 wt-%, or at least 3 wt-%, or at least 4 wt-%, based on the total weight of the uncoated particle core. One or more binders can be used in an amount of up to 10 wt-%, or up to 9 wt-%, or up to 8 wt-%, or up to 7 wt-%, or up to 6 wt-%, based on the total weight of the uncoated particle core. In certain embodiments, the particle cores of the capsules of the present disclosure include 3 wt-% to 7 wt-% binder(s), based on the total weight of an uncoated particle core. In certain embodiments, the particle cores of the capsules of the present disclosure include 4 wt-% to 6 wt-% binder(s), based on the total weight of an uncoated particle core.

Particles described herein can further include a stabilizer, preferably in the core. Suitable stabilizers for use in the particle core include, but are not limited to, calcium hydroxide, calcium carbonate, sodium bicarbonate, magnesium carbonate, and other alkali or alkaline earth metal hydroxides and carbonates. Combinations of stabilizers can be used if desired. Preferably, calcium carbonate is used as a stabilizer.

One or more stabilizers can be used in an amount of at least 1 wt-%, or at least 2 wt-%, based on the total weight of the particle core. One or more stabilizers can be used in an amount of up to 10 wt-%, or up to 5 wt-%, based on the total weight of the particle core. In certain embodiments, the particle cores of the capsules of the present disclosure include 2 wt-% to 10 wt-% stabilizer(s), based on the total weight of an uncoated particle core.

Suitable release controlling agents for use in the coating on the particle core include, but are not limited to, ethylcellulose, polyvinyl acetate, polyacrylate and polymethacrylate (e.g., Ammonio Methacrylate Copolymer, Type A and Type B; Ethyl Acrylate and Methyl Methacrylate Copolymer), and copolymers thereof. Combinations of release controlling agents can be used if desired. Preferably, ethylcellulose (such as that available from The Dow Chemical Company under the trade designation ETHOCEL Standard 10 Premium) is used as a release controlling agent.

One or more release controlling agents can be used in an amount of at least 45 wt-%, or at least 50 wt-%, or at least 55 wt-%, or at least 60 wt-%, based on the total weight of the coating. One or more release controlling agents can be used in an amount of up to 80 wt-%, or up to 70 wt-%, or up to 65 wt-%, or up to 62 wt-%, based on the total weight of the coating. In certain embodiments, the particle coatings include 55 wt-% to 65 wt-% release control agent(s), based on the total weight of the coating. In certain embodiments, the particle coatings include 60 wt-% to 62 wt-% release control agent(s), based on the total weight of the coating.

Herein, "based on the total weight of the coating" means the total weight of the non-volatile components of the coating (e.g., release controlling agent, pore former, and plasticizer).

Pore formers that are suitable for use in the coating formulation include, but are not limited to, hypromellose, hydroxypropyl cellulose, methylcellulose, hydroxyethylcellulose, carboxymethylcellulose, sodium carboxymethylcellulose, polyethylene glycol, guar gum, xanthan gum, sodium alginate, povidone (i.e., polyvinylpyrrolidone), crospovidone, sodium starch glycolate, croscarmellose sodium, starch (e.g., pregelatinized starch), carbohydrates (e.g., mannitol, glucose, sucrose, fructose, mannose, galactose, sorbitol, and dextran), sodium chloride, potassium chloride, and calcium chloride. Preferred pore formers for use in the coating on the particle core include, but are not limited to, hydroxypropyl methylcellulose ("HPMC" such as hypromellose 2910 USP available under the trade name METHOCEL E5 Premium, METHOCEL E15 Premium), carboxymethylcellulose, methylcellulose, croscarmellose sodium, povidone, sodium starch glycolate, starch (e.g., pregelatinized starch), alginic acid, guar gum, and polyethylene glycol. Combinations of pore formers can be used if desired. Preferably, hydroxypropyl methylcellulose (hypromellose 2910) is used as a pore former (such as that available from The Dow Chemical Company under the trade designation METHOCEL E5 Premium).

One or more pore formers can be used in an amount of at least 5 wt-%, or at least 10 wt-%, or at least 15 wt-%, or at least 20 wt-%, or at least 22 wt-%, based on the total weight of the coating. One or more pore formers can be used in an amount of up to 30 wt-%, or up to 26 wt-%, or up to 25 wt-%, or up to 24 wt-%, based on the total weight of the coating. In certain embodiments, the particle coatings include 20 wt-% to 25 wt-% pore former(s), based on the total weight of the coating. In certain embodiments, the particle coatings include 22 wt-% to 24 wt-% pore former(s), based on the total weight of the coating.

Suitable plasticizers for use in the coating on the particle core include, but are not limited to, diethyl phthalate, triethyl citrate, dibutyl sebacate, polyethylene glycol, triacetin, tributyl citrate, glycerol, and propylene glycol. Combinations of plasticizers can be used if desired. Preferably, diethyl phthalate is used as a plasticizer.

One or more plasticizers can be used in an amount of at least 5 wt-%, or at least 10 wt-%, or at least 15 wt-%, based on the total weight of the coating. One or more plasticizers can be used in an amount of up to 30 wt-%, or up to 20 wt-%, or up to 18 wt-%, based on the total weight of the coating. In certain embodiments, the particle coatings include 10 wt-% to 20

wt-% plasticizer(s), based on the total weight of the coating. In certain embodiments, the particle coatings include 15 wt-% to 18 wt-% plasticizer(s), based on the total weight of the coating.

The coating solution typically includes the "solids" or non-volatile components (e.g., ethylcellulose, hypromellose 2910 and diethyl phthalate) along with solvents, such as a mixture of alcohol and water, such that the concentration of the non-volatile components in the coating solution is 5 wt-% to 10 wt-%. In an exemplary solution, the solvents are dehydrated alcohol and purified water in a weight ratio of 3.7:1.

Particles can be coated with a coating composition as described herein using conventional techniques known to one of skill in the art. Briefly, such coating techniques include bottom-spray fluid-bed coating (e.g., Würster), top-spray fluid-bed coating, and tangential-spray fluid-bed coating. Typically, such methods result in a coating that is substantially uniform on each individual particle.

An amount of coated particles sufficient to deliver the desired dose may be encapsulated into a capsule of any desirable size, for example, a size 000, 00, 0e1, 0, 1, 2, 3, 4, or 5.

Components of a suitable capsule shell include, but are not limited to, hydroxypropyl methylcellulose and gelatin. Preferably, a capsule shell is a hydroxypropyl methylcellulose (HPMC) shell (e.g., at least 90 wt-% HPMC, based on the weight of the shell). Typically, commercially available HPMC capsules include small amounts of water, colorants (e.g., TiO_2 and iron oxides), and optionally gelling agents and gelling promoters. They have relatively low moisture content, making them suitable for moisture-sensitive materials. Such capsules resist breakage even at low moisture levels. HPMC capsules typically exhibit low solubility in ethanol, particularly in acidic media such as found in the stomach. Encapsulation of the particles of the present disclosure in such an HPMC capsule shell preferably reduces dose dumping (and immediate release) of topiramate from the coated particles (see "Alcohol Dose Dumping" experiment in the Examples Section).

The chemical stability of capsules of the present disclosure typically depends on humidity and/or water activity. Thus, it can be desirable to reduce exposure to excessive moisture during storage. This can be done, for example, by storing the capsules of the present disclosure in a container, particularly a sealed container that includes a desiccant. If a desiccant is used, the ratio of weight of desiccant to weight of filled capsules can be at least 0.01, or at least 0.1, or at least 0.25, and can be up to 0.9.

Suitable containers include, for example, high density polyethylene (HDPE). Such containers can be bottles with screw caps, or the like. Preferably, such bottles are sealed, particularly induction sealed, in addition to a boundary layer provided by the screw cap.

Suitable desiccants include, for example, silica gel, bentonite clay, and molecular sieve. Combinations of desiccants can be used if desired.

Capsules of the present disclosure are preferably chemically stable. That is, capsules of the present disclosure retain a potency of at least 90% after a given time period of storage in a sealed container at 25° C. and 60% relative humidity (RH). They also demonstrate little or no decomposition after a given time period such that no more than 2000 parts per million (ppm) each of sulfate or sulfamate decomposition products are produced (see Examples Section). In this context, the given time period is preferably at least 12 months (typically, without any packaging), or at least 24 months (potentially, without any packaging, although packaging, e.g., sealed container and desiccant as described herein would be preferred to achieve chemical stability for this length of time), or at least 36 months (typically, with packaging, e.g., sealed container and desiccant as described herein).

The present disclosure also provides methods of dosing a subject in need thereof. Such dosing could be for the treatment of convulsions (e.g., convulsions associated with epilepsy). Such dosing could be for prophylactic treatment, for example, of a migraine. Such dosing methods include administering a topiramate capsule. In certain embodiments, once-per-day dosing of the capsule of the present disclosure occurs in the morning. In certain embodiments, once-per-day dosing of the capsule of the present disclosure occurs in the evening.

In certain embodiments, the extended-release topiramate capsules of the present disclosure, when dosed to a healthy human subject once daily (e.g., in the morning or evening), achieves at steady-state, an $AUC_{0\text{-}24h}$, C_{max}, and C_{min}) in the subject's plasma that are within the 80% to 125% bioequivalence criteria compared to immediate-release topiramate dosed twice per day (where the once-daily dose contains 2× the topiramate active agent as the individual immediate-release doses).

In this context, two treatments are bioequivalent at steady state (i.e., they are not different from one another) if the 90% confidence interval (CI) of the least squares geometric mean of one formulation-to-another formulation (e.g., capsules of the present disclosure to once-daily dose topiramate) ratio for each pharmacokinetic (PK) parameter (e.g., $AUC_{0\text{-}24h}$, C_{max}, and C_{min}) is completely contained within the 80-125% interval.

In certain embodiments, the extended-release topiramate capsules of the present disclosure, when dosed to a healthy human subject once daily in the morning, achieves at steady-state, a reduction of fluctuation index of at least 15% compared to immediate-release topiramate dosed twice per day. In certain embodiments, the reduction of fluctuation index is at least 20% compared to immediate-release topiramate dosed twice per day. In certain embodiments, the reduction of fluctuation index is at least 25% compared to immediate-release topiramate dosed twice per day.

In certain embodiments, the extended-release topiramate capsules of the present disclosure, when dosed to a healthy human subject once daily in the morning, achieves at steady-state, a C_{min} in the subject's plasma that is higher than the C_{min} compared to immediate-release topiramate dosed twice per day.

In certain embodiments, the extended-release topiramate capsules of the present disclosure, when given as a single-dose to a healthy human subject, achieves an $AUC_{0\text{-}inf}$ of 170 to 210 h·μg/mL within a 95% confidence interval, and a C_{max} of 2 to 4 μg/mL within a 95% confidence interval.

Capsules of the present disclosure demonstrate a reduced level of side effects compared to other topiramate products. For example, in certain embodiments, the extended-release topiramate capsules of the present disclosure, when dosed once daily to a population of human patients suffering from epilepsy, achieves a reduction in incidence of at least one side effect compared to immediate-release topiramate dosed at the same total daily dose divided twice per day. This comparison is based on the extended-release topiramate capsules of the present disclosure compared to placebo, and the immediate-release topiramate (TOPAMAX) compared to placebo. The term "incidence" refers to the percentage of patients who experience a new side effect during the study. The at least one side effect includes somnolence, dizziness, ataxia, disturbance in attention, memory impairment, cognitive disorder, and psychomotor slowing.

LIST OF EXEMPLARY EMBODIMENTS

1. An extended-release topiramate capsule comprising:
   a capsule shell comprising (or consisting essentially of, or consisting of) a single population of coated particles;
   wherein each coated particle comprises a core and a coating thereon;
   wherein each particle core comprises a homogeneous mixture comprising topiramate throughout its core; and
   wherein the coating comprises one or more release controlling agent(s).

2. The capsule of embodiment 1 wherein:
   each particle core comprises a homogeneous mixture comprising:
   topiramate;
   one or more filler(s); and
   one or more binder(s); and
   the coating comprises:
   one or more release controlling agent(s);
   one or more pore former(s); and
   one or more plasticizer(s).

3. An extended-release topiramate capsule comprising (or consisting essentially of, or consisting of):
   a capsule shell comprising (or consisting essentially of, or consisting of) a single population of coated particles;
   wherein each coated particle comprises (or consists essentially of, or consists of) a core and a coating thereon;
   wherein each particle core comprises (or consists essentially of, or consists of) a homogeneous mixture throughout its core, the mixture comprising (or consisting essentially of, or consisting of):
   40 wt-% to 50 wt-% of topiramate, based on the total weight of an uncoated particle core;
   45 wt-% to 55 wt-% of one or more filler(s), based on the total weight of an uncoated particle core; and
   3 wt-% to 7 wt-% of one or more binder(s), based on the total weight of an uncoated particle core;
   wherein the coating comprises (or consists essentially of, or consists of):
   55 wt-% to 65 wt-% of one or more release control agent(s), based on the total weight of the coating;
   20 wt-% to 25 wt-% of one or more pore former(s), based on the total weight of the coating; and
   10 wt-% to 20 wt-% of one or more plasticizer(s), based on the total weight of the coating;
   wherein the particles are coated in an amount sufficient to provide a weight gain of 8% to 14%.

4. The extended-release topiramate capsule of any of embodiments 1 through 3 wherein the particles are coated in an amount sufficient to provide a weight gain of 10% to 12%.

5. The extended-release topiramate capsule of any of embodiments 1 through 4 wherein the one or more filler(s) is selected from the group of microcrystalline cellulose, dibasic calcium phosphate, lactose, tribasic calcium phosphate, mannitol, and combinations thereof.

6. The extended-release topiramate capsule of embodiment 5 wherein the filler is microcrystalline cellulose.

7. The extended-release topiramate capsule of any of embodiments 1 through 6 wherein the one or more binder(s) is selected from the group of hydroxypropyl methylcellulose, methylcellulose, carboxymethylcellulose, sodium carboxymethylcellulose, hydroxypropyl cellulose, hydroxyethylcellulose, polyvinyl pyrrolidine, starch, natural gum, and combinations thereof.

8. The extended-release topiramate capsule of embodiment 7 wherein the binder is hydroxypropyl methylcellulose.

9. The extended-release topiramate capsule of any of embodiments 1 through 8 wherein the one or more release controlling agent(s) is selected from the group of ethylcellulose, polyvinyl acetate, polyacrylate and polymethacrylate, copolymers thereof, and combinations thereof.

10. The extended-release topiramate capsule of embodiment 9 wherein the release controlling agent is ethylcellulose.

11. The extended-release topiramate capsule of any of embodiments 1 through 10 wherein the one or more pore former(s) is selected from the group of hypromellose, hydroxypropyl cellulose, methylcellulose, hydroxyethylcellulose, carboxymethylcellulose, sodium carboxymethylcellulose, polyethylene glycol, guar gum, xanthan gum, sodium alginate, polyvinylpyrrolidone, crospovidone, sodium starch glycolate, croscarmellose sodium, starch, mannitol, glucose, sucrose, fructose, mannose, galactose, sorbitol, dextran, sodium chloride, potassium chloride, calcium chloride, and combinations thereof.

12. The extended-release topiramate capsule of embodiment 11 wherein the pore former is hydroxypropyl methylcellulose.

13. The extended-release topiramate capsule of any of embodiments 1 through 12 wherein the one or more plasticizer(s) is selected from the group of diethyl phthalate, triethyl citrate, dibutyl sebacate, polyethylene glycol, triacetin, tributyl citrate, glycerol, propylene glycol, and combinations thereof.

14. The extended-release topiramate capsule of embodiment 13 wherein the plasticizer is diethyl phthalate.

15. The extended-release topiramate capsule of any of embodiments 1 through 14 wherein each particle core further comprises one or more stabilizer(s).

16. The extended-release topiramate capsule of embodiment 15 wherein the one or more stabilizer(s) is selected from the group of calcium hydroxide, calcium carbonate, sodium bicarbonate, magnesium carbonate, and combinations thereof.

17. The extended-release topiramate capsule of embodiment 15 or 16 wherein the one or more stabilizer(s) is present in an amount of 2 wt-% to 10 wt-%, based on the total weight of an uncoated particle core.

18. An extended-release topiramate capsule comprising (or consisting essentially of, or consisting of):
   a capsule shell comprising (or consisting essentially of, or consisting of) a single population of coated particles;
   wherein each coated particle comprises (or consists essentially of, or consists of) a core and a coating thereon;
   wherein each particle core comprises (or consists essentially of, or consists of) a homogeneous mixture throughout its core, the mixture comprising (or consisting essentially of, or consisting of):
   40 wt-% to 50 wt-% of topiramate, based on the total weight of an uncoated particle core;
   45 wt-% to 55 wt-% of one or more filler(s), based on the total weight of an uncoated particle core; wherein the one or more filler(s) is selected from the group of microcrystalline cellulose, dibasic calcium phosphate, lactose, tribasic calcium phosphate, mannitol, and combinations thereof; and
   3 wt-% to 7 wt-% of one or more binder(s), based on the total weight of an uncoated particle core; wherein the one or more binder(s) is selected from the group of hydroxypropyl methylcellulose, methylcellulose, carboxymethylcellulose, sodium car-

boxymethylcellulose, hydroxypropyl cellulose, hydroxyethylcellulose, polyvinyl pyrrolidine, starch, natural gum, and combinations thereof;

wherein the coating comprises (or consists essentially of, or consists of):

55 wt-% to 65 wt-% of one or more release control agent(s), based on the total weight of the coating; wherein the one or more release controlling agent(s) is selected from the group of ethylcellulose, polyvinyl acetate, polyacrylate and polymethacrylate, copolymers thereof, and combinations thereof;

20 wt-% to 25 wt-% of one or more pore former(s), based on the total weight of the coating; wherein the one or more pore former(s) is selected from the group of hypromellose, hydroxypropyl cellulose, methylcellulose, hydroxyethylcellulose, carboxymethylcellulose, sodium carboxymethylcellulose, polyethylene glycol, guar gum, xanthan gum, sodium alginate, polyvinylpyrrolidone, crospovidone, sodium starch glycolate, croscarmellose sodium, starch, mannitol, glucose, sucrose, fructose, mannose, galactose, sorbitol, dextran, sodium chloride, potassium chloride, calcium chloride, and combinations thereof; and

10 wt-% to 20 wt-% of one or more plasticizer(s), based on the total weight of the coating; wherein the one or more plasticizer(s) is selected from the group of diethyl phthalate, triethyl citrate, dibutyl sebacate, polyethylene glycol, triacetin, tributyl citrate, glycerol, propylene glycol, and combinations thereof;

wherein the particles are coated in an amount sufficient to provide a weight gain of 8% to 14%.

19. An extended-release topiramate capsule comprising (or consisting essentially of, or consisting of):

a capsule shell comprising (or consisting essentially of, or consisting of) a single population of coated particles;

wherein each coated particle comprises (or consists essentially of, or consists of) a core and a coating thereon;

wherein each particle core comprises (or consists essentially of, or consists of) a homogeneous mixture throughout its core, the mixture comprising (or consisting essentially of, or consisting of):

40-50 wt-% of topiramate, based on the total weight of an uncoated particle core;

45-55 wt-% of microcrystalline cellulose, based on the total weight of an uncoated particle core; and

3-7 wt-% of hydroxypropyl methylcellulose, based on the total weight of an uncoated particle core;

wherein the coating comprises (or consists essentially of, or consists of):

55-65 wt-% of ethylcellulose, based on the total weight of the coating;

20-25 wt-% of hydroxypropyl methylcellulose, based on the total weight of the coating; and

10-20 wt-% of diethyl phthalate, based on the total weight of the coating;

wherein the particles are coated in an amount sufficient to provide a weight gain of 8% to 14%.

20. An extended-release topiramate capsule comprising (or consisting essentially of, or consisting of):

a capsule shell comprising (or consisting essentially of, or consisting of) a single population of coated particles;

wherein each coated particle comprises (or consists essentially of, or consists of) a core and a coating thereon;

wherein each particle core comprises (or consists essentially of, or consists of) a homogeneous mixture throughout its core, the mixture comprising (or consisting essentially of, or consisting of):

44-46 wt-% of topiramate, based on the total weight of an uncoated particle core;

48-52 wt-% of microcrystalline cellulose, based on the total weight of an uncoated particle core; and

4-6 wt-% of hydroxypropyl methylcellulose, based on the total weight of an uncoated particle core;

wherein the coating comprises (or consists essentially of, or consists of):

60-62 wt-% of ethylcellulose, based on the total weight of the coating;

22-24 wt-% of hydroxypropyl methylcellulose, based on the total weight of the coating; and

15-18 wt-% of diethyl phthalate, based on the total weight of the coating;

wherein the particles are coated in an amount sufficient to provide a weight gain of 10-12%.

21. The extended-release topiramate capsule of any of embodiments 1 through 20 which, when dosed to a healthy human subject once daily (e.g., in the morning or evening), achieves at steady-state, an $AUC_{0\text{-}24h}$, C_{max}, and C_{min} in the subject's plasma that are within the 80% to 125% bioequivalence criteria compared to immediate-release topiramate dosed twice per day.

22. The extended-release topiramate capsule of any of embodiments 1 through 21 which, when dosed to a healthy human subject once daily in the morning, achieves at steady-state, a reduction of fluctuation index of at least 15% compared to immediate-release topiramate dosed twice per day.

23. The extended-release topiramate capsule of embodiment 22 which, when dosed to a healthy human subject once daily in the morning, achieves at steady-state, a reduction of fluctuation index of at least 20% compared to immediate-release topiramate dosed twice per day.

24. The extended-release topiramate capsule of embodiment 23 which, when dosed to a healthy human subject once daily in the morning, achieves at steady-state, a reduction of fluctuation index of at least 25% compared to immediate-release topiramate dosed twice per day.

25. The extended-release topiramate capsule of any of embodiments 1 through 24 which, when dosed to a healthy human subject once daily in the morning, achieves at steady-state, a C_{min} in the subject's plasma that is higher than the C_{min} compared to immediate-release topiramate dosed twice per day.

26. The extended-release topiramate capsule of any of embodiments 1 through 25 which, when given as a single-dose to a healthy human subject, achieves an $AUC_{0\text{-}inf}$ of 170 to 210 h·μg/mL within a 95% confidence interval, and a C_{max} of 2 to 4 μg/mL within a 95% confidence interval.

27. The extended-release topiramate capsule of any of embodiments 1 through 26 which, when dosed once daily to a population of human patients suffering from epilepsy, achieves a reduction in incidence of at least one side effect compared to immediate-release topiramate dosed at the same total daily dose divided twice per day.

28. The extended-release topiramate capsule of any of embodiments 1 through 27 which is chemically stable for at least 12 months.

29. The extended-release topiramate capsule of embodiment 28 which is chemically stable for at least 24 months.

30. The extended-release topiramate capsule of embodiment 29 which is chemically stable for at least 24 months when stored in a sealed container with desiccant.

31. The extended-release topiramate capsule of embodiment 30 which is chemically stable for at least 36 months when stored in a sealed container with desiccant.
32. The extended-release topiramate capsule of any of embodiments 1 through 31 which is free of an immediate release component.
33. The extended-release topiramate capsule of any of embodiments 1 through 32 wherein the coated particles have a sphericity of at least 0.7.
34. The extended-release topiramate capsule of any of embodiments 1 through 33 wherein the coated particles have a particle size of at least 500 μm.
35. The extended-release topiramate capsule of any of embodiments 1 through 34 wherein the coated particles have a particle size of up to 1300 μm.
36. The extended-release topiramate capsule of any of embodiments 1 through 35 wherein the capsule shell comprises hydroxypropyl methylcellulose or gelatin.
37. The extended-release topiramate capsule of embodiment 36 wherein the capsule shell is a hydroxypropyl methylcellulose capsule.
38. A container comprising an extended-release topiramate capsule of any of embodiments 1 through 37 and desiccant.
39. The container of embodiment 38 wherein the ratio of weight of desiccant to weight of filled capsules is at least 0.01.
40. The container of embodiment 38 or 39 wherein the ratio of weight of desiccant to weight of filled capsules is up to 0.9.
41. The container of any of embodiments 38 through 40 wherein the desiccant is selected from silica gel, bentonite clay, molecular sieve, and combinations thereof.
42. A method of dosing a subject in need thereof, the method comprising administering an extended-release topiramate capsule of any of embodiments 1 through 37 once daily to the subject.
43. The method of embodiment 42 wherein the administering occurs once daily in the morning.
44. The method of embodiment 42 wherein the administering occurs once daily in the evening.
45. The method of any of embodiments 42 through 44 wherein the dosing is for the treatment of convulsions.
46. The method of any of embodiments 42 through 44 wherein the dosing is for the prophylactic treatment of a migraine.

EXAMPLES

Process and Formulations

1. High Shear Granulation: The core bead components listed in the table below are added to the high shear granulator and blended. After the pre-mix step, Purified Water is added to the high shear granulator and the mixture kneaded to create a wet granulation.
2. Extrusion: The wet granulation is then fed at a specified rate into a twin dome extruder equipped with dome dies having 0.8 mm pores to form an extrudate.
3. Spheronization: Portions of the extrudate from the extruder are weighed out and processed, for a specified time sufficient to form spherical particles (i.e., beads), in a spheronizer equipped with a 2×2 mm friction plate.
4. Drying: The wet spherical particles are dried in a fluid bed processor to a moisture content of not more than (NMT) 3.0% w/w, as determined by an in-process loss-on-drying analysis.
5. Sizing: The dried particles are sized using a 14-mesh and a 30-mesh sieve (Market Grade mesh screen). Material passing through the 14-mesh sieve, but retained on the 30-mesh sieve is taken into the subsequent coating step.
6. Coating: The dried, sized, uncoated beads are coated in a Wiirster fluidized bed processor to a desired coating weight gain using the coating composition listed in the table below.
7. Sizing: Following coating, the beads are sized using a 14-mesh and a 30-mesh sieve (Market Grade mesh screen). Material passing through the 14-mesh sieve, but retained on the 30-mesh sieve is taken into the subsequent encapsulation step.
8. Encapsulation: Using a suitable encapsulator, appropriate amounts of coated beads are filled into appropriate size capsules to yield the different strengths of the product. The encapsulated product is also run through a capsule polisher, metal detector, and weight checker.

	Formulation designation	
	A	B
Coating Weight Gain**	12% w/w	10% w/w
Core particle components (% w/w, based on weight of the core)		
Topiramate	45	45
Microcrystalline Cellulose	50	50
Hypromellose 2910	5	5
Coating components*** (% w/w, based on weight of the coating)		
Ethylcellulose	60.86	60.86
Hypromellose 2910	22.56	22.56
Diethyl Phthalate	16.58	16.58
Dehydrated Alcohol*	NA	NA
Purified Water*	NA	NA

*Removed during processing.
**Weight gain is defined as the theoretical weight gain after coating of a population of uncoated particles, assuming 100% coating efficiency.
***The solids content (non-volatile components, i.e., ethylcellulose, hypromellose 2910 and diethyl phthalate) of the coating solution was 7.5% w/w for B and 6% w/w for A. The ratio of Dehydrated Alcohol to Purified Water is about 3.7:1 on a weight basis.

PK Results

In clinical studies, the extended-release topiramate capsules of Formulation A, when given as a single-dose to a healthy human subject, achieved an $AUC_{0\text{-}inf}$ of 173.9 to 200.1 h·μg/mL within a 95% confidence interval, and a C_{max} of 2.64 to 3.16 μg/mL within a 95% confidence interval.

In clinical studies, the extended-release topiramate capsules of Formulation B, when given as a single-dose to a healthy human subject, achieved an $AUC_{0\text{-}inf}$ of 179.7 to 204.3 h·μg/mL within a 95% confidence interval, and a C_{max} of 2.94 to 3.43 μg/mL within a 95% confidence interval.

Adverse Event Evaluation

In clinical studies, the extended-release topiramate capsules of the present disclosure, when dosed to patients with epilepsy (more specifically, as adjunctive treatment in patients with refractory partial onset seizure with or without generalization) once daily, achieved a reduction in incidence of at least one side effect compared to immediate-release topiramate dosed at the same total daily dose divided twice per day.

This comparison is based on the extended-release topiramate capsules of the present disclosure compared to placebo, and the immediate-release topiramate (TOPAMAX) compared to placebo. Each being compared to placebo (as opposed to each other), this evaluation demonstrated that the extended-release topiramate capsules of the present disclosure achieve a reduction in at least one side effect (e.g., somnolence, dizziness, ataxia, disturbance in attention, memory impairment, cognitive disorder, and psychomotor slowing).

Alcohol Dose Dumping

Capsules of the present disclosure, which included an ethanol-soluble particle coating, were evaluated in vitro for dose dumping in ethanol using a USP apparatus 1 (baskets) operating at 100 revolutions per minute (rpm) with a pH 1.2 HCl buffer containing 5 to 40% v/v (volume by volume) ethanol. There was no evidence of immediate release or unacceptable acceleration of release of the topiramate.

Sulfate/Sulfamate Method

Sulfate and Sulfamate degradation products were measured utilizing an ion chromatography (IC) method with ion suppression conductivity detection. The chromatographic system used an Alltech Novosep A-2, 250×4.0 mm, 5-μm particle size column maintained at 43° C. The flow rate of the 3.6 mM sodium carbonate mobile phase was 1.0 mL/min. A 7 mg/mL solution of topiramate in water containing 10% acetonitrile was prepared from particles (removed from a capsule of the present disclosure) using sonication and mixing to extract the sulfate and sulfamate degradation products. Particles within the capsules of the present disclosure demonstrated little or no decomposition after a given time period, such that no more than 2000 parts per million (ppm) each of sulfate or sulfamate degradation products were produced.

The complete disclosures of the patents, patent documents, and publications cited herein are incorporated by reference in their entirety as if each were individually incorporated. Various modifications and alterations to this disclosure will become apparent to those skilled in the art without departing from the scope and spirit of this disclosure. It should be understood that this disclosure is not intended to be unduly limited by the illustrative embodiments and examples set forth herein and that such examples and embodiments are presented by way of example only with the scope of the disclosure intended to be limited only by the claims set forth herein as follows.

What is claimed is:

1. An extended-release topiramate capsule comprising:

a capsule shell comprising a single population of coated particles;

wherein each coated particle comprises a core and a coating thereon;

wherein each particle core comprises a homogeneous mixture throughout its core, the mixture comprising:

10 wt-% to 80 wt-% of topiramate, based on the total weight of an uncoated particle core;

10 wt-% to 85 wt-% of one or more filler(s), based on the total weight of an uncoated particle core; and

1 wt-% to 10 wt-% of one or more binder(s), based on the total weight of an uncoated particle core;

wherein the coating comprises:

45 wt-% to 80 wt-% of one or more release controlling agent(s), based on the total weight of the coating;

5 wt-% to 30 wt-% of one or more pore former(s), based on the total weight of the coating; and

5 wt-% to 30 wt-% of one or more plasticizer(s), based on the total weight of the coating;

wherein, when a single dose is given to a healthy human subject, an $AUC_{0\text{-}inf}$ of 170 to 210 h·μg/mL within a 95% confidence interval, and a C_{max} of 2 to 4 μg/mL within a 95% confidence interval are achieved in the subject's plasma.

2. The extended-release topiramate capsule of claim **1** which, when dosed to a healthy human subject once daily, achieves at steady-state, an $AUC_{0\text{-}24h}$, C_{max}, and C_{min} in the subject's plasma that are within the 80% to 125% bioequivalence criteria compared to immediate-release topiramate dosed at the same total daily dose divided twice per day.

3. The extended-release topiramate capsule of claim **1** which, when dosed to a healthy human subject once daily in the morning, achieves at steady-state, a reduction of fluctuation index of at least 15% compared to immediate-release topiramate dosed at the same total daily dose divided twice per day.

4. The extended-release topiramate capsule of claim **1** which, when dosed to a healthy human subject once daily in the morning, achieves at steady-state, a C_{min} in the subject's plasma that is higher than the C_{min} compared to immediate-release topiramate dosed at the same total daily dose divided twice per day.

5. The extended-release topiramate capsule of claim **1** which, when dosed once daily to a population of human patients suffering from epilepsy, achieves a reduction in incidence of at least one side effect compared to immediate-release topiramate dosed at the same total daily dose divided twice per day.

6. The extended-release topiramate capsule of claim **1** wherein the particles are coated in an amount sufficient to provide a weight gain of 2% to 30%.

7. The extended-release topiramate capsule of claim **1** which is chemically stable for at least 12 months.

8. The extended-release topiramate capsule of claim **1** wherein the capsule shell is a hydroxypropyl methylcellulose capsule.

9. The extended-release topiramate capsule of claim **1** which is free of an immediate-release component.

10. The extended-release topiramate capsule of claim **1** wherein the one or more filler(s) is selected from the group of microcrystalline cellulose, dibasic calcium phosphate, lactose, tribasic calcium phosphate, mannitol, and combinations thereof.

11. The extended-release topiramate capsule of claim **10** wherein the filler is microcrystalline cellulose.

12. The extended-release topiramate capsule of claim **1** wherein the one or more binder(s) is selected from the group of hydroxypropyl methylcellulose, methylcellulose, carboxymethylcellulose, sodium carboxymethylcellulose, hydroxypropyl cellulose, hydroxyethylcellulose, polyvinyl pyrrolidine, starch, natural gum, and combinations thereof.

13. The extended-release topiramate capsule of claim **12** wherein the binder is hydroxypropyl methylcellulose.

14. The extended-release topiramate capsule of claim **1** wherein the one or more release controlling agent(s) is selected from the group of ethylcellulose, polyvinyl acetate, polyacrylate and polymethacrylate, copolymers thereof, and combinations thereof.

15. The extended-release topiramate capsule of claim **14** wherein the release controlling agent is ethylcellulose.

16. The extended-release topiramate capsule of claim **1** wherein the one or more pore former(s) is selected from the group of hypromellose, hydroxypropyl cellulose, methylcellulose, hydroxyethylcellulose, carboxymethylcellulose, sodium carboxymethylcellulose, polyethylene glycol, guar gum, xanthan gum, sodium alginate, polyvinylpyrrolidone, crospovidone, sodium starch glycolate, croscarmellose sodium, starch, mannitol, glucose, sucrose, fructose, mannose, galactose, sorbitol, dextran, sodium chloride, potassium chloride, calcium chloride, and combinations thereof.

17. The extended-release topiramate capsule of claim **16** wherein the pore former is hydroxypropyl methylcellulose.

18. The extended-release topiramate capsule of claim **1** wherein the one or more plasticizer(s) is selected from the group of diethyl phthalate, triethyl citrate, dibutyl sebacate, polyethylene glycol, triacetin, tributyl citrate, glycerol, propylene glycol, and combinations thereof.

19. The extended-release topiramate capsule of claim 18 wherein the plasticizer is diethyl phthalate.

20. The extended-release topiramate capsule of claim 1 wherein each particle core further comprises one or more stabilizer(s) selected from the group of calcium hydroxide, calcium carbonate, sodium bicarbonate, magnesium carbonate, and combinations thereof.

21. An extended-release topiramate capsule comprising:

a capsule shell comprising a single population of coated particles;

wherein each coated particle comprises a core and a coating thereon;

wherein each particle core comprises a homogeneous mixture throughout its core,

the mixture comprising:

10 wt-% to 80 wt-% of topiramate, based on the total weight of an uncoated particle core;

10 wt-% to 85 wt-% of one or more filler(s), based on the total weight of an uncoated particle core; wherein the one or more filler(s) is selected from the group of microcrystalline cellulose, dibasic calcium phosphate, lactose, tribasic calcium phosphate, mannitol, and combinations thereof; and

1 wt-% to 10 wt-% of one or more binder(s), based on the total weight of an uncoated particle core; wherein the one or more binder(s) is selected from the group of hydroxypropyl methylcellulose, methylcellulose, carboxymethylcellulose, sodium carboxymethylcellulose, hydroxypropyl cellulose, hydroxyethylcellulose, polyvinyl pyrrolidine, starch, natural gum, and combinations thereof;

wherein the coating comprises:

45 wt-% to 80 wt-% of one or more release control agent(s), based on the total weight of the coating; wherein the one or more release controlling agent(s) is selected from the group of ethylcellulose, polyvinyl acetate, polyacrylate and polymethacrylate, copolymers thereof, and combinations thereof;

5 wt-% to 30 wt-% of one or more pore former(s), based on the total weight of the coating; wherein the one or more pore former(s) is selected from the group of hypromellose, hydroxypropyl cellulose, methylcellulose, hydroxyethylcellulose, carboxymethylcellulose, sodium carboxymethylcellulose, polyethylene glycol, guar gum, xanthan gum, sodium alginate, polyvinylpyrrolidone, crospovidone, sodium starch glycolate, croscarmellose sodium, starch, mannitol, glucose, sucrose, fructose, mannose, galactose, sorbitol, dextran, sodium chloride, potassium chloride, calcium chloride, and combinations thereof; and

5 wt-% to 30 wt-% of one or more plasticizer(s), based on the total weight of the coating; wherein the one or more plasticizer(s) is selected from the group of diethyl phthalate, triethyl citrate, dibutyl sebacate, polyethylene glycol, triacetin, tributyl citrate, glycerol, propylene glycol, and combinations thereof;

wherein, when a single dose is given to a healthy human subject, an $AUC_{0\text{-}inf}$ of 170 to 210 h·μg/mL within a 95% confidence interval, and a C_{max} of 2 to 4 μg/mL within a 95% confidence interval are achieved in the subject's plasma.

22. The extended-release topiramate capsule of claim 21 which, when dosed to a healthy human subject once daily, achieves at steady-state, an $AUC_{0\text{-}24h}$, C_{max}, and C_{min} in the subject's plasma that are within the 80% to 125% bioequivalence criteria compared to immediate-release topiramate dosed at the same total daily dose divided twice per day.

23. The extended-release topiramate capsule of claim 21 which, when dosed to a healthy human subject once daily in the morning, achieves at steady-state a reduction of fluctuation index of at least 15% compared to immediate-release topiramate dosed at the same total daily dose divided twice per day.

24. The extended-release topiramate capsule of claim 21 which, when dosed to a healthy human subject once daily in the morning, achieves at steady-state a C_{min} in the subject's plasma that is higher than the C_{min} compared to immediate-release topiramate dosed at the same total daily dose divided twice per day.

25. The extended-release topiramate capsule of claim 21 which, when dosed once daily to a population of human patients suffering from epilepsy, achieves a reduction in incidence of at least one side effect compared to immediate-release topiramate dosed at the same total daily dose divided twice per day.

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